

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

SANOFI-AVENTIS U.S. LLC,)	
)	
Plaintiff,)	
)	
v.)	Civil Action No. 10-01255 (ABJ)
)	
FOOD AND DRUG ADMINISTRATION,)	
<i>et al.</i> ,)	
)	
Defendants.)	
)	

MEMORANDUM OPINION

Plaintiff sanofi-aventis U.S. LLC (“Sanofi”) brought this action against the Food and Drug Administration (“FDA”), its Commissioner of Food and Drugs, Margaret A. Hamburg, and the Secretary of Health and Human Services, Kathleen Sebelius, alleging that FDA exceeded its statutory authority under the Federal Food, Drug, and Cosmetic Act (“FDCA”) and unlawfully departed from agency precedent when it approved a generic version of the Sanofi drug Lovenox. Sandoz, Inc. (“Sandoz”), the manufacturer of the generic drug, intervened as a defendant, and now the parties have cross-moved for summary judgment. The Court concludes that 1) the FDA acted within its statutory authority when it called for Sandoz to file immunogenicity data as part of its abbreviated new drug application; 2) it did not unlawfully depart from agency precedent by approving a generic before the listed drug had been fully characterized; and 3) it reasonably found that the active ingredient in the generic drug was the same as the active ingredient in Lovenox. Therefore, plaintiff’s motion for summary judgment will be denied, and defendants’ cross-motions will be granted.

BACKGROUND

I. Statutory Background

The FDCA requires all new drugs to be approved by the FDA before they are introduced into interstate commerce. 21 U.S.C. § 355(a). It provides two primary pathways for obtaining approval: (1) the new drug application (“NDA”), described in section 355(b); and (2) the abbreviated new drug application (“ANDA”) for generic products set forth in section 355(j).

A drug that follows the NDA pathway is referred to as a “pioneer” drug because it is the first drug of its kind to go through an approval process with the FDA. The NDA procedure requires the applicant to conduct a spectrum of safety and effectiveness tests and to inform the FDA of the results. The information that must be provided with an NDA includes in relevant part: “full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use,” § 355(b)(1)(A); “a full list of the articles used as components . . .” and “a statement of the composition...” of the drug, § 355(b)(1)(B)–(C); and, “a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug,” § 355(b)(1)(D). Once the drug is approved, it is referred to as a “listed drug.” *See* 21 C.F.R. § 314.3(b).

In some cases, a new drug applicant may seek to rely on research conducted by a third party in order to meet the approval requirements.¹ In that instance, the statute sets out a procedure under section 355(b)(2), which requires the applicant to file additional information showing that the drug’s approval will not infringe a valid patent. 21 U.S.C. § 355(b)(2).

¹ The statute specifies that this pathway is to be utilized when “[a]n application submitted under paragraph (1) for a drug for which the investigations [demonstrating safety and effectiveness] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and . . . the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.” 21 U.S.C. § 355(b)(2).

Congress added the truncated ANDA approval process to the FDCA as part of the 1984 Hatch-Waxman amendments, which sought “to make available more low cost generic drugs” by providing a pathway that was less costly and time consuming than the NDA process. *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1316 (D.C. Cir. 1998), citing H.R. REP. NO. 98-857, pt. 1, at 14 (1984). ANDA applicants must file information showing that the conditions of use, active ingredient, dosage form, strength, route of administration, and labeling of the generic drug are “the same as” those of the reference listed drug (“RLD”)² that was previously approved.³ 21 U.S.C. § 355(j)(2)(A)(i)–(iii), (v). They are thereby relieved of the obligation to supply the extensive testing demonstrating safety and effectiveness that is the hallmark of the NDA process, *see* § 355(b)(1)(A), but ANDA applicants are still required to supply the other information required of a new drug applicant. *See* § 355(j)(2)(A)(vi) (“An abbreviated application for a new drug shall contain – . . . (vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section[.]”). This means the ANDA applicant must list the components and composition of the generic drug, and must provide “a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug” § 355(b)(1)(a)(D), incorporated into requirements for ANDA applications by § 355(j)(2)(A)(vi).

2 A “reference listed drug,” or RLD, is “the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application.” 21 C.F.R. § 314.3(b).

3 Part of this opinion concerns the showing to be made under section 355(j)(2)(A)(ii) that the generic drug’s active ingredient is “the same as” the RDL’s active ingredient, which will be referred to as the showing of “active ingredient sameness.” The statute also requires a showing of bioequivalence, *see* § 355(j)(2)(A)(iv), which Sanofi defines as “the absence of a significant difference in the rate and extent to which the active ingredient in a pharmaceutical equivalent or alternative becomes available at the site of drug action, when administered at the same does, under similar conditions, in an appropriately designed study,” Sanofi’s Mem. at vi. Bioequivalence is not contested in this case.

But, in accordance with Congress’s goal to keep the ANDA pathway less costly and time consuming than the NDA pathway, the statute expressly prohibits the FDA from requiring ANDA applicants to submit any other categories of information. § 355(j)(2)(A), (j)(4). Section 355(j)(2)(A) provides: “The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).” In addition, the statute limits the FDA’s discretion to reject an ANDA. § 355(j)(4). Section 355(j)(4) mandates that “the Secretary shall approve” an ANDA “unless” he or she makes certain specified findings, including that the generic drug’s active ingredient is not the same as the listed drug’s active ingredient, or that “the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality and purity[.]” § 355(j)(4).

II. Factual Background⁴

A. Sanofi and Lovenox

Sanofi owns the NDA for the injectable anti-coagulation drug Lovenox, which was approved by FDA in 1993. AR 2881–82. The active ingredient in Lovenox is a compound called enoxaparin sodium (“enoxaparin”). AR 2882. Enoxaparin is made up of a core protein from which an assortment of different sugar chains, known as oligosaccharide chains, extend. AR 5, 12, 2882. To date, no one has fully determined enoxaparin’s complete chemical makeup, or fully “characterized” it, because the sugar chains are too difficult to identify, and the relative abundance of the different chains varies from batch to batch of enoxaparin. AR 10–12, 2904.

⁴ The factual background is also laid out in great detail in the Court’s preliminary injunction opinion, *Sanofi-Aventis U.S. LLC v. FDA*, 733 F. Supp. 2d 162, 164–66 (D.D.C. 2010).

Apparently, this variation is common among compounds in the class of anticoagulants that enoxaparin belongs to, called low molecular weight heparins. AR 2884.

On February 19, 2003, Sanofi submitted a Citizen Petition⁵ urging FDA to withhold approval of any ANDA for generic enoxaparin “[u]ntil such time as enoxaparin has been fully characterized . . . unless the manufacturing process used to create the generic product is determined to be equivalent to [Sanofi’s] manufacturing process for enoxaparin, or the application is supported by proof of equivalent safety and effectiveness demonstrated through clinical trials.”⁶ AR 1. FDA ultimately rejected this request to forestall the marketing of a generic.⁷ AR 2878–2922.

Instead, FDA found that “enoxaparin has been adequately characterized for the purposes of approving . . . generic enoxaparin,” and it articulated a five-pronged test to be used to determine whether the active ingredient in any proposed generic version of Lovenox would be

5 A citizen petition is a document submitted to FDA by a third party under 21 C.F.R. § 10.30, which requests that FDA take or refrain from taking a particular action.

6 At the motions hearing, counsel for Sanofi assured the Court, “if a generic applicant were able – and this is clearly laid out in the Citizens Petition – if a generic applicant were able to fully characterize themselves enoxaparin and lay out their product and lay out Sanofi’s product and say, look, it matches up, matches up, matches up, that would be sufficient.” Tr. 42. But counsel then acknowledged that “it could not be done under current technology.” Tr. 43. Sanofi’s position has been, then, that a generic version of Lovenox could only be approved at some unspecified point in the future when the technology necessary for characterization has evolved. Tr. 43. Absent that, according to Sanofi, a generic should be subject to the full range of NDA testing for safety and effectiveness, or its manufacturing process should be shown to be identical to the RLD’s. Tr. 43–44.

7 Sanofi also asked FDA to reject any application for generic enoxaparin that did not show the drug to contain a certain type of sugar chain (1,6 anhydro ring structure) in similar concentrations to Lovenox. AR 1. Sanofi identified that chain as important to enoxaparin’s overall pharmacological effect. AR 1. FDA accepted this part of the Citizen Petition. AR 2879–80.

the same as the enoxaparin in Lovenox.⁸ AR 2879–80. According to FDA, “each of [the five prongs] captures different aspects of the active ingredient’s ‘sameness.’” AR 2879–80.

The record indicates that when the five-pronged approach was under consideration, there was a difference of opinion among two internal FDA units. AR 3836. While the Office of Generic Drugs (“OGD”) supported the test, the Office of New Drug Quality Assessment (“ONDQA”) argued that the test was insufficient, and that the only way to show active ingredient sameness would be to fully characterize enoxaparin. AR 3836. The determination to adopt the test was made by the Deputy Director of the Office of Pharmaceutical Science, Center for Drug Evaluation and Research, who, in a memorandum that thoroughly considered both sides’ arguments, found the five-pronged test to be sufficient. AR 3836–61.

B. Sandoz

On August 26, 2005, while Sanofi’s Citizen Petition was pending, Sandoz filed an ANDA for generic enoxaparin. *See* AR 4440. FDA approved the ANDA on July 23, 2010, and it rejected Sanofi’s Citizen Petition the same day. AR 4440–44. The approval process took just under five years, and it included lengthy exchanges between Sandoz and FDA as well as multiple amendments to the ANDA. *See* AR 4440-44.

At issue here is FDA’s request, two years into the approval process, for information regarding the potential of Sandoz’s proposed drug to elicit an adverse immune response (its immunogenicity). AR 4167–73. In making its request, FDA relied on studies showing that enoxaparin has been known to cause a dangerous immune response in certain patients, called

⁸ These five prongs address: (1) “the physical and chemical characteristics of enoxaparin”; (2) “the nature of the source material and the method used to break up the polysaccharide chains into smaller fragments”; (3) “the nature and arrangement of components that constitute enoxaparin”; (4) “certain laboratory measurements of anticoagulant activity”; and (5) “certain aspects of the drug’s effect in humans,” meaning the *in vivo* pharmacodynamics profile, which is based upon its effects on two factors, anti-Xa and anti-IIa. AR 2880, 2899.

thrombocytopenia, which can be life-threatening. AR 3848–49, 3853. Importantly, the cause of thrombocytopenia is complex. AR 3854. Although enoxaparin itself can stimulate thrombocytopenia, it may also be stimulated by impurities in the drug. AR 2918, 3848–49, 3853–54. Furthermore, impurities may affect the strength of the reaction when it occurs. AR 2918, 3854.

In a November 5, 2007 letter to Sandoz, FDA concluded that its ANDA was “not approvable because the application does not adequately address the potential for immunogenicity of the drug product.” AR 4167. FDA required Sandoz to either amend the ANDA so that it addressed that deficiency or to withdraw the application. AR 4167 In a December 4, 2007 follow-up letter, FDA explained its decision, informing Sandoz that its amended ANDA should address the impurity profile of its generic enoxaparin and suggesting several approaches. AR 4170–74. The letter stated:

FDA is particularly concerned with product and process derived impurities that may modify the biological activity or enhance the immunogenicity of your product. Understanding the potential for your product to elicit an immune response is critical, since low molecular weight heparins are associated with a serious immune-driven adverse event, heparin induced thrombocytopenia (HIT). Impurities can interact either with the product or with the host immune system in ways that alter outcome. Thus, for products that have the potential for immunologic adverse events and certainly for products with known immunologic adverse events, the contribution of impurities needs to be carefully considered.

AR 4170. FDA asked Sandoz to address three concerns:

- The ability of its generic drug to bind to and form complexes with the compound PF4, relative to Lovenox. FDA asserted that one known cause of thrombocytopenia is the presence of certain dangerous complexes that are formed when enoxaparin binds to PF4. Furthermore, impurities are known to facilitate the creation of these harmful complexes. Since Sandoz had sufficiently shown that the enoxaparin in its generic drug was the same as in Lovenox, comparative information about the ability of its generic drug to bind to and form these enoxaparin-PF4 complexes relative to Lovenox would shed light on whether the generic drug contains any harmful impurities.

- The amount and nature of potential product contaminants (innate immune agonists) in its generic drug, relative to those in Lovenox.
- The functional immunogenic properties of the generic drug, relative to Lovenox (*i.e.*, its actual effect on immune response). FDA explained that this could be tested by in vitro assays or animal models that would show the immune response elicited by the generic drug as compared to Lovenox.

AR 4170–73.

In response, Sandoz provided FDA with data from laboratory tests that compared the immunity profile and immunogenicity of its generic enoxaparin to Lovenox. AR 4181–90. The results submitted compared Sandoz’s generic to Lovenox with regard to: “(a) the ability of enoxaparin to form complexes with PF4, (b) the presence of impurities that could stimulate the immune system directly, (c) activation of human PBMC, and (d) the induction of antibodies to the product in mice.” AR 4433; *see also* AR 4181–90.

Based on all the information that Sandoz submitted, including the immunogenicity data, and its application of the five-pronged test described above, FDA found that “Sandoz’s ANDA for enoxaparin sodium injection [met] the requirements for ANDA approval, including those regarding active ingredient sameness and purity of the proposed drug.” AR 4437–38.

III. Procedural background

On July 26, 2010, Sanofi filed this action against FDA. Compl. [Dkt. # 1]. Count I alleges that FDA exceeded its authority under the FDCA, in violation of the APA, by requiring Sandoz to submit the immunogenicity data as part of its ANDA. Compl. ¶¶ 37–42. Count II alleges that FDA departed from agency precedent in violation of the APA by approving Sandoz’s ANDA before enoxaparin had been fully characterized. Compl. ¶¶ 43–46. Count III alleges that FDA exceeded its authority under the FDA and acted contrary to established agency precedent in violation of the APA by approving Sandoz’s ANDA without sufficient evidence that the active

ingredient in Sandoz's generic enoxaparin was "the same as" the active ingredient in Lovenox. Compl. ¶¶ 47–51.

On the same day it filed its complaint, Sanofi filed a motion seeking a temporary restraining order ("TRO") and preliminary injunction ("PI") to compel FDA to withdraw approval of Sandoz's ANDA pending a trial on the merits. Pl.'s Mot. for TRO and PI [Dkt. # 3]. After consolidating the TRO and PI, the Court denied them both, relying in part on its finding that Sanofi was unlikely to succeed on the merits of any of the three claims. *Sanofi-Aventis U.S. LLC*, 733 F. Supp. 2d at 162.

On July 28, 2010, the Court granted Sandoz's motion for leave to intervene as a defendant. Sandoz's Mot. to Intervene [Dkt. # 6]. The parties have now cross-moved for summary judgment on all counts.

STANDARD OF REVIEW

Summary judgment is appropriate "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). The party seeking summary judgment bears the "initial responsibility of informing the district court of the basis for its motion, and identifying those portions of the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, which it believes demonstrate the absence of a genuine issue of material fact." *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986) (internal quotation marks omitted). To defeat summary judgment, the non-moving party must "designate specific facts showing that there is a genuine issue for trial." *Id.* at 324 (internal quotation marks omitted). The existence of a factual dispute is insufficient to preclude summary judgment. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247–48 (1986). A dispute is "genuine" only if a reasonable fact-finder could find for the

nonmoving party; a fact is only “material” if it is capable of affecting the outcome of the litigation. *Id.* at 248. *See also Laningham v. U.S. Navy*, 813 F.2d 1236, 1241 (D.C. Cir. 1987).

“The rule governing cross-motions for summary judgment . . . is that neither party waives the right to a full trial on the merits by filing its own motion; each side concedes that no material facts are at issue only for the purposes of its own motion.” *Sherwood v. Wash. Post*, 871 F.2d 1144, 1148 n.4 (D.C. Cir. 1989), quoting *McKenzie v. Sawyer*, 684 F.2d 62, 68 n.3 (D.C. Cir. 1982). In assessing each party’s motion, “[a]ll underlying facts and inferences are analyzed in the light most favorable to the non-moving party.” *N.S. ex rel. Stein v. District of Columbia*, 709 F. Supp. 2d 57, 65 (D.D.C. 2010), citing *Anderson*, 477 U.S. at 247.

ANALYSIS

I. FDA did not exceed its authority under the FDCA by requiring Sandoz to submit immunogenicity data as part of its ANDA.

The first question at issue here – whether FDA had the authority to require Sandoz to submit immunogenicity data for generic enoxaparin as part of its ANDA – can be decided on summary judgment because it is a pure question of statutory interpretation. Plaintiff cites section 355(j)(2)(A) – the provision that prevents FDA from requiring ANDA applicants to submit information not listed in the statute – and it asks the Court to declare that FDA exceeded its authority under the FDCA, acted arbitrarily and capriciously, and abused its discretion by calling for the comparative test results, thereby violating the APA, 5 U.S.C. § 706(2)(A), (C). Compl. ¶¶ 37–42.

A. The *Chevron* framework for the review of FDA action

The APA establishes the scope of judicial review of agency action, and the standard of review under the APA is quite narrow. *See Vermont Yankee Nuclear Power Corp. v. Natural Res. Def. Council, Inc.*, 435 U.S. 519, 545–49 (1978),

The Court is required to analyze an agency's interpretation of a statute by following the two-step procedure set forth in *Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984). First, the Court must determine "whether Congress has directly spoken to the precise question at issue." *Id.* at 842. "If the intent of Congress is clear, that is the end of the matter, for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Id.* at 842–43. Courts "use 'traditional tools of statutory construction' to determine whether Congress has unambiguously expressed its intent," *Serono Labs., Inc., v. Shalala*, 158 F.3d 1313, 1319 (D.C. Cir. 1998), including an examination of the statute's text, structure, purpose, and legislative history. *Bell Atl. Tel. Co. v. FCC*, 131 F.3d 1044, 1047 (D.C. Cir. 1997).

If the Court concludes that the statute is either silent or ambiguous, the second step of the review process is to determine whether the interpretation proffered by the agency is "based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843. Once a reviewing court reaches the second step, it must accord "considerable weight" to an executive agency's construction of a statutory scheme it has been "entrusted to administer." *Id.* at 844. Indeed, "under *Chevron*, courts are bound to uphold an agency interpretation as long as it is reasonable – regardless whether there may be other reasonable, or even more reasonable, views." *Serono*, 158 F.3d at 1321. And the court must defer to an agency's reading of its own regulations unless it is "plainly erroneous or inconsistent with the regulation." *Id.* at 1320 (internal quotation marks omitted).

Using this framework, the Court reaffirms the determinations that were made when the motion for preliminary injunction was denied: first, that the FDCA does not speak directly to the precise question of whether the FDA may require the submission of comparative

immunogenicity data as part of an ANDA; and second, that the FDA’s interpretation of the FDCA to permit it to require such data was reasonable. *Sanofi-Aventis*, 733 F. Supp. 2d at 168–71. Since the statute does not plainly prohibit the agency from requesting the data as plaintiff suggests, plaintiff’s motion for summary judgment on Count I on *Chevron I* grounds must be denied. Rather, the statute is sufficiently broad such that the agency is authorized to make its own judgment about what kinds of data fall within the broad categories of information it is statutorily permitted to require and what kinds of data it needs to make the expert assessment it is statutorily entrusted to make. Accordingly, granting the agency the *Chevron II* deference to which it is therefore entitled, the Court finds that the request for the test results was reasonable, and it will enter judgment for the defendants on Count I.

B. Chevron Step I

Sanofi argues that the FDCA expressly provides that the FDA may not require ANDA applicants to provide any information beyond the eight categories of information listed by Congress in section 355(j)(2)(A)(i)–(viii), and that immunogenicity testing is simply not included in those categories.⁹ Pl.’s Mem. in Supp. of Mot. for Summ. J. (“Pl.’s Mem”) at 17 [Dkt. # 38]. Therefore, it submits that the agency lacked the authority to require the test results

⁹ The notion that section (j)(2)(A) should be read strictly to deprive the agency of the authority to call for the tests is plaintiff’s core contention: counsel directed the Court’s attention to the provision repeatedly during the hearing and even cited it as the grounds for why the agency’s interpretation was flawed under *Chevron* step II. See Tr. at 4, 5, 12, 15, 17–19, 26–27, 30, 57, and 84.

as part of its consideration of the application, and it should have denied the application – or assessed it under section 355(b)(2) – instead.¹⁰

FDA and Sandoz respond by pointing out that one of the categories listed in section (j)(2)(A) for ANDA applications – section (j)(2)(A)(vi) – specifically incorporates provisions from the list set forth in section 355(b)(1) for new drug applications, including section (b)(1)(D). FDA’s Mem. in Supp. of Cross Mot. for Summ. J. (“FDA’s Mem.”) at 5 [Dkt. # 40]; Sandoz’s Mem. in Supp. of Cross Mot. for Summ. J. (“Sandoz’s Mem.”) at 11 [Dkt. # 43]. They locate FDA’s authority to seek the comparative testing in that provision, which directs an applicant to supply “a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of [the] drug.” FDA’s Mem. at 5, quoting 21 U.S.C. § 355(b)(1)(D).

Sanofi submits, fairly, that those words do not literally appear to encompass test results comparing the potential adverse effects of a generic drug to the pioneer. Pl.’s Mem. at 19. Therefore, the Court cannot enter judgment for the defendants without going beyond the *Chevron* step I stage.

Defendants note that the statute requires FDA to approve an ANDA unless it determines that “the methods used in, or the facilities and controls used for, the manufacturing, processing and packing of the drug are inadequate to assure and preserve its identity, strength and purity.” 21 U.S.C. § 355(j)(4)(A). In other words, Congress required the agency to assess purity, and the things the agency may demand be fully described under section (b)(1)(D) are the very things the agency must deem to be adequate to ensure the purity of the drug. So, the defendants maintain

10 Of course, as defendant Sandoz points out, denial of the ANDA would have extended Sanofi’s seventeen-year monopoly in the market for enoxaparin. Sandoz’s Mem. in Supp. of Cross Mot. for Summ. J. (“Sandoz’s Mem.”) at 3 [Dkt. # 43]. But it is that economic interest in the RLD that gives Sanofi standing to complain in this case.

that the agency is authorized to interpret the requirement of a “full description” of the methods and controls called for by section 355(b)(1)(D) to encompass the information it needs to make the findings required by section 355(j)(4)(A) – and indeed, that the words “full description” must be read as a means to accomplish that purpose. *See, e.g.,* FDA Cross Mot. for Summ. J. at 5–6.

For the reasons to be set forth in more detail below, the Court agrees. Through the ANDA pathway’s specific embrace of the NDA requirements, and the imposition of the clear demands in section 355(j)(4)(A), Congress rendered the ANDA requirements to be ambiguous and open to agency interpretation, and not as restrictive as the plaintiffs describe them to be. By specifically incorporating section 355(b)(1)(D) into the ANDA requirements, Congress gave FDA the authority to utilize its expertise to determine what information it needs to make the assessment it is required to make under section 355(j)(4)(A).

1. Circuit precedent suggests that the statute is ambiguous, and that the agency has been entrusted with its interpretation.

The Court’s conclusion is supported by guidance provided in *Serono Laboratories, Inc. v. Shalala*, 158 F.3d at 1324–25, where the Court of Appeals indicated that the clauses enumerating what the FDA may review in an ANDA should be construed broadly. In *Serono*, a pharmaceutical company filed an ANDA for a generic version of Serono’s drug Pergonal, and Serono opposed it with a Citizen Petition. *Id.* at 1316. The FDA questioned whether the concentration of a certain inactive ingredient in the generic drug raised safety concerns, and in making the ultimate decision that it did not, the agency reviewed three animal studies that the ANDA applicant had submitted as part of its application. *Id.* at 1323–4. As in this case, the manufacturer of the pioneer drug objected to the consideration of the test results. *Id.* at 1324. Among other questions in the case, then, the court was asked to address whether the FDA had the statutory authority to consider animal studies submitted as part of an abbreviated application.

The Court of Appeals observed:

The only provision of the Act to which Serono points for support of its no-animal-studies proposition is one that states the FDA “may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)” of 21 U.S.C. § 355(j)(2)(A). Because nothing in those clauses mentions animal studies, Serono contends they are barred. This provision, however, does not bear the weight Serono applies.

Id. at 1324 (internal citations omitted). The same principle applies here.

Serono argued that section 355(j)(2)(A) of the FDCA barred FDA from considering animal studies because they did not fall within the of types of information enumerated in sections 355(j)(2)(A)(i)–(viii) that the agency is permitted to require. *Id.* Ultimately, the court did not reach the issue because it based its holding on a circumstance not present in this case: it ruled that even if the provision did prohibit the FDA from *requiring* an applicant to submit animal studies, “[i]t does not bar an applicant from voluntarily submitting additional information – including animal studies – as part of its ANDA.”¹¹ *Id.* at 1324. But the Court went on to observe that the interpretation being advanced by the NDA holder was too restrictive:

[T]he indicated clauses do not suggest that animal studies are in any way disfavored. The clauses simply describe what the “information” in an application must “show.” They do not specify the kinds of studies that can or cannot be used to satisfy the requirement.

Id. The Court then cited one of the categories in section 355(j)(2)(A) – “An abbreviated application for a new drug shall contain . . . information to show that the active ingredients of the new drug are the same as those of the listed drug” – as an example of one of the clauses that

11 Sandoz argues that FDA did not actually “require” it to submit the immunogenicity information. Sandoz Opp. at 14 [Dkt. No. #20]. While it is true that FDA purported to suggest the kinds of information that would address their three concerns without telling Sandoz what exactly to file, the Court will proceed on the premise that the information was actually required because FDA plainly refused to accept Sandoz’s ANDA without the information. AR 4170.

identified a broad category of required information but did not specify how it was to be fulfilled. *Id.*

While these observations may not have been necessary to the ruling in *Serono*, they express a clear view that section 355(j)(2)(A) does not limit the agency’s freedom to determine what kinds of information will be needed to fulfill the listed ANDA requirements.

Sanofi attempts to distinguish *Serono* on the grounds that the tests FDA required here were justified under section 355(b)(1)(D)’s call for a “full description” of manufacturing processes and controls, incorporated into the ANDA requirements in section 355(j)(2)(A)(vi), and not under the clauses contained in sections 355(j)(2)(A)(i)–(v), which contain the language referenced by the Court that authorizes FDA to require “information to show” certain characteristics of the generic drug. Pl.’s Reply to Opp. to Mot. for TRO and PI (“Pl.’s Reply”) at 8–12 [Dkt. # 21]. But this Court does not find the concept expressed in *Serono* to be tied to a parsing of the words “information” or “show” in particular, or to be limited to the first five categories set out in section 355(j)(2)(A) rather than all eight. The Court of Appeals simply cited one of the categories listed in section 355(j)(2)(A) as an example of the ANDA statutory requirements. *Id.* (“See, e.g., id. § 355(j)(2)(A)(ii)(II)”)(emphasis added).

The *Serono* court indicated that it was considering the larger question of whether the (j)(2)(A) prohibition against requiring “information in addition to that required by clauses (i) through (viii)” should be narrowly construed to bar particular forms of information not specifically mentioned in the eight categories. *See id.* at 1324. It answered the question by drawing a distinction between the broad requirement set forth in each section and “the kinds of studies that can or cannot be used to satisfy the requirement.” *Id.* That differentiation applies equally to the “full description” of processes and controls called for by the incorporation of

section 355(b)(1)(D) into section 355(j)(2)(A)(vi). Like the section of the ANDA provisions analyzed in *Serono*, the section at issue here, section 355(b)(1)(D), “do[es] not specify the kinds of studies that can or cannot be used to satisfy the requirement.” *Id.* And the terms “full description” are sufficiently broad to warrant the same treatment as “information to show.”

2. An analysis of the text in light of the entire statutory scheme suggests that the statute is ambiguous.

On that point, it is important to remember that the first step of the *Chevron* analysis requires the Court to look not only at the words in question, but at the entire statute. And the text at issue here – the statutory requirement that an ANDA applicant must supply a “full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of [the] drug” – comes straight from the new drug requirements. 21 U.S.C. § 355(b)(1)(D). This means there was a deliberate legislative choice to import some of the new drug pathway requirements into the ANDA pathway *verbatim*. There is no dispute that in the context of a new drug application, the statutory requirements are to be construed broadly. *See* Tr. at 11. And, as counsel for *Sanofi* agreed at the hearing, there is no basis to construe the words differently when they are incorporated into the list of ANDA requirements. *Id.*¹² *see Ratzlaf v. United States*, 510 U.S. 135, 143 (1994) (“A term appearing in several places in a statutory text is generally read the same way each time it appears.”).

Furthermore, an analysis of the provisions in question in the context of the entire statute requires that section 355(j)(2)(A) be viewed in light of section 355(j)(4)(A), which specifies that

12 “The Court: My question is simply that the words – you said this is a statutory argument, they’ve said this is a statutory argument – the words mean the same thing whether we’re talking about a new drug or an ANDA, right?

A: Yes, they do.

Q: And in the case of a new drug, you have to read them broadly, don’t you?

A: Yes, your Honor.”

“the Secretary shall approve an application for a drug unless the Secretary finds the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity.”¹³ Through this section, Congress has directed the FDA to satisfy itself that the processes utilized by the ANDA applicant will “assure” quality and purity, but none of the categories of information the agency may require that are listed in section 355(j)(2)(A) expressly provide for the submission of any information demonstrating quality or purity. This apparent contradiction is another source of the ambiguity that propels the Court from step one of the *Chevron* analysis to step two.

Moreover, the fact that section 355(j)(4)(A) parallels section 355(b)(1)(D) suggests that Congress intended them to be read together. *See United Savings Ass’n of Tex. v. Timbers of Inwood Forest Assocs.*, 484 U.S. 365, 371 (1988) (“A provision that may seem ambiguous in isolation is often clarified by the remainder of the statutory scheme – because the same terminology is used elsewhere in a context that makes its meaning clear, or because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law.”) (citations omitted). While Sanofi is correct that section 355(j)(4)(A) does not expand the scope of what FDA may require in an ANDA, it does shed light on *why* Congress wanted FDA to look at the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of a generic drug: in part, to ensure the drug’s quality and purity.

13 Sanofi mischaracterizes this language, arguing that “[b]y its plain language, this Section simply says that FDA must *reject* an ANDA application if it finds that the limited information required by section [355](b)(1)(D) is ‘inadequate’ to assure the product’s purity.” Pl.’s Mem. at 28; Pl.’s Reply at 9. The Court notes that this section does not require rejection if the *information* submitted falls short; it requires *approval* unless, given all the information submitted, FDA makes a determination that the methods, facilities, and controls *themselves* are inadequate to assure purity.

Sanofi does not disagree with that much of the analysis.¹⁴ *See* Tr. at 7, 16. But it insists that section 355(b)(1)(D) should be interpreted strictly to mean that an applicant can only be asked to “describe” its manufacturing methods and controls for that purpose, and not to report on tests that would reveal the effect of those methods and controls on the purity of the product. Pl.’s Mem. at 26.

But reading the provision in light of the statutory scheme as a whole militates against this approach. First of all, the words “full description” themselves do not support plaintiff’s rigid position, and the fact that the ANDA requirement is lifted from the NDA requirements compels a broad reading. Finally, the fact that Congress described the agency’s task in 355(j)(4)(A) utilizing the same words found in 355(b)(1)(D) lends meaning to the imprecise words used in that section and indicates that now that they have been transplanted into the ANDA requirements, they must be interpreted as a means to facilitate, and not frustrate, the statutorily mandated evaluation of the purity of a proposed generic drug.

14 The Court: My question to you is, we’ve agreed that the FDA has to think about purity?
Counsel for plaintiff: Yes, your Honor.

Q: So which of the eight does it fall under, which of the things it can require is going to give it that information?

A: We are not in disagreement over this point. We believe Subsection vi, which incorporates (b)(1)(D) is the section in which Congress delineated what FDA is permitted to require and so we think that is the core provision that this Court is called upon to interpret.

Tr. at 7.

* * *

Q: Well, doesn’t (j)(4)(A) and the fact that it tracks the language from 355(b)(1)(D) suggest that if there’s any purpose to be served by the full description requirement in (b)(1)(D) at all, its purpose is to illuminate issues such as quality and purity?

A: Yes. That is the purpose of this information so that FDA can make the determination

Tr. at 16.

Sanofi argues that FDA's request for the immunogenicity information was improper because it went beyond a request to compare the impurity content of Sandoz's generic drug with that of Lovenox, but asked Sandoz to assess whether any difference in impurities would increase the likelihood of adverse consequences and thus be harmful to consumers. Pl.'s Mem. at 53–54. It is true that FDA required some of the studies in order to show whether the difference in the impurity profiles of Sandoz's generic drug and Lovenox made the generic more likely to cause immune responses than Lovenox.¹⁵ See AR 4170–73, 4433. But FDA did not call for the sort of safety and effectiveness tests that are part of an NDA and excluded from the ANDA process; the tests were expressly requested to answer questions about the purity of the product. See AR 4170. And, as counsel for Sandoz pointed out at the motions hearing, if one reads section 355(j)(4)(A) within the context of the ANDA amendments as a whole, it is clear that the (j)(4) assessment necessarily involves a comparison of the generic to the listed drug.

Counsel for Sandoz: . . . I guess what I would say is, first of all if you look at (j)(4)(A) and it says that FDA has to make findings with respect to manufacturing, processing, packaging, methods and controls adequate, among other things, to assure purity. Now, (j)(4)(A) doesn't say the words "in comparison to the brand," but I think given the whole context of the Hatch-Waxman provisions, it has to be implicit. And that's the whole nature of this.

Q: Otherwise, what difference would purity make?

A: That's right. It's only in comparison to the brand. If the brand has a certain level of impurity and you are at or below that level, you're okay. If you come in with a product that's otherwise the same but your impurity levels are ten times higher than the brand, well that's an inquiry that the FDA has to make, and you're not going to get approved under that scenario as a true generic under (j).

Tr. at 77–78.

¹⁵ At the hearing, defendants asserted that there is no assertion by any party that the generic drug is in fact more harmful or impure than the pioneer. The issue here is simply about process. Tr. at 79–81, 85–86. Sanofi did not contest that assertion. *Id.*

A close reading of the statute suggests that the argument can be put more strongly, and that the comparative nature of the inquiry is not merely implicit, but expressed, in the ANDA provisions. Congress directed FDA to determine whether the generic manufacturer's processes and controls were adequate not only to "assure," but to "preserve" the drug's "identity, strength, quality, and purity." 21 U.S.C. § 355(j)(4)(A). Since section 355(j)(4) is talking about the approval of generic copies of listed drugs, the purity to be "preserved" must be the purity of the original. So a comparison of the adverse effects caused by impurities is warranted. And the directive that the FDA be confident that the processes are adequate to assure not only the quality, but the "identity" of the generic also indicates that the (j)(4)(A) assessment – to be based on the (b)(1)(D) "full description" – is a comparative one. Under those circumstances, the statute did not prohibit the solicitation of comparative tests.

3. An analysis of the text in light of the statute's purpose suggests that the statute is ambiguous.

The *Chevron* step I exercise also involves a consideration of the provisions at issue in light of the statute's purpose. See *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1067–68 (D.C. Cir. 1998), quoting *Pilot Life Ins. Co. v. Dedeaux*, 481 U.S. 41, 51 (1987) ("[I]n expounding a statute, we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law, and to its object and policy."). Sanofi cited *Mova Pharmaceutical, id.*, and *Schering Corp. v. FDA*, 51 F.3d 390 (3d Cir. 1995), and maintained that "these statutes are entry-restricting statutes." Tr. at 28. But the legislative history and the text of the statute point to the opposite conclusion, and the precedents Sanofi cites do not address the situation here.

While certain terms of the Hatch-Waxman amendments may have been the result of a legislative compromise as plaintiff suggested, see Tr. at 51, and they may reflect the balancing of

the interests of manufacturers of listed drugs, would-be marketers of generics, and consumers, the clear purpose of the amendments is set out in the very first sentence of the House Report: “The purpose of Title I of the bill is to make available more low cost generic drugs by establishing a generic drug approval procedure” H. REP. NO. 98-857(1), pt. 1, at 1 (1984). The instruction in section 355(j)(2) that FDA may call for no categories of information beyond those enumerated in the statute must be read as a means to fulfill this purpose – to keep the agency from delaying or impeding the ANDA approval process by placing additional demands on the applicants. This reading is borne out by the language of section 355(j)(4), which embodies a congressional preference in favor of ANDA approval.

Neither *Schering Corp.* nor *Mova Pharmaceutical* compels a different conclusion. Both cases raise the market entry concept only in the context of a ruling on the pioneer manufacturer's standing, and both found particular provisions – not the statute as a whole or the provisions at issue here – to be barriers to market entry. In *Schering Corp.*, the court found that the bioequivalence requirement contained in section 355(j)(7)(B) is meant to restrict market entry, and therefore, the plaintiff, whose economic position would be injured by the approval of a generic competitor, had standing to challenge the regulations implementing that provision. 51 F.3d at 396. And in *Mova Pharmaceutical*, the Court of Appeals was looking only at section 355(j)(5)(B)(iv), the provision that accords priority among successive ANDA applicants. It simply noted that the statutory provision that regulates the timing of generic drug manufacturers' entry into the marketplace would also have the effect of freeing the pioneer drug manufacturer from competition as well, so the pioneer company had grounds to intervene in the action. 140 F.3d at 1076–77.

In sum, considering section 355(j)(2)(A) in the context of the entire statutory scheme and the statute’s purpose, the Court finds the NDA provision that is included in section (j)(2)(A) – section (b)(1)(D) – to be ambiguous for *Chevron* step I purposes. Given the ambiguity in the statute and this Circuit’s direction that courts should construe the clauses in section 355(j)(2)(A) broadly, this Court cannot hold that the FRCA unambiguously precludes FDA from requiring immunogenicity data in an ANDA.

C. Chevron Step II

At *Chevron* step II, the Court must ask whether the FDA’s interpretation of section 355(b)(1)(d) is “based on a permissible construction of the statute,” *Chevron*, 467 U.S. at 843, and consistent with the statute’s text and overall scheme, *see Nat’l Ass’n of Home Builders v. Defenders of Wildlife*, 551 U.S. 644, 666 (2007). As noted above, the Court must defer to FDA’s interpretation of the statute if its interpretation is reasonable.

Here, FDA sought tests that compared the immunogenicity of the generic to the parent, and it specified that the tests were sought to alleviate its concerns about purity. AR 4170. In *Serono*, the D.C. Circuit underscored that deference is particularly appropriate when FDA approval of drugs is involved. 158 F.3d at 1324. It cited the holding in *Schering Corp.* that “judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA’s expertise and merit deference from us.” *Id.*, quoting *Schering Corp.*, 51 F.3d at 399. Since section 355(j)(4) expressly calls upon the agency to assess the purity of a generic, *see* § 355(j)(4)(A), as well its safety and efficacy, *see* § 355(j)(4)(F),(H), the *Schering* observation approved by this Circuit is equally applicable to a situation where the agency made a judgment as to what was required to ascertain the purity of a drug. FDA’s close and careful review of the scientific information – its approval of Sandoz’s application took

nearly five years – is further grounds for deference. *See* Tr. at 81; *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218–19 (D.D.C. 1996) (seven-year comprehensive review of scientific testing merits deference).

According FDA the deference required under *Serono* to make its own determination about the information it might need, the Court finds that FDA’s interpretation of the ANDA approval regime was reasonable, and that it was reasonable for the agency to conclude that immunogenicity studies are encompassed by the “full description” described in section 355(b)(1)(D).¹⁶ The potential for the generic drug to elicit a different adverse response than the parent could be the result of impurities, which in turn result from the methods, facilities, and controls used to manufacture, process, and pack a drug. By revealing what impurities remain at the end of that process, the studies shed light on, or indirectly “describe,” those methods and controls.

FDA maintains that its call for test results was also fully consistent with its regulations. The Court must defer to the agency’s reading of its own regulations unless it is “plainly erroneous or inconsistent with the regulation,” *Serono*, 158 F.3d at 1320 (internal quotation marks omitted), and in this case, the Court cannot make such a finding. The FDA regulations implementing the ANDA approval provisions in the statute describe the information applicants must provide to the agency to fulfill each of the requirements listed in section 355(j)(2)(A). *See* 21 C.F.R. § 314.94. For the “chemistry, manufacturing, and controls” called for by section (j)(2)(A)’s invocation of section (b)(1)(D), though, the ANDA regulations require applicants to submit “the information required under section 314.50(d)(1),” which is the regulation governing

¹⁶ Indeed, Sanofi said very little about why the agency’s interpretation would be unreasonable other than to repeat its *Chevron* step I argument that the immunogenicity tests fell outside the list of items FDA could require under section 355(j)(2)(A). Tr. at 19–20.

new drug applications. 21 C.F.R. § 314.94(a)(9)(i). And that regulation makes it clear that the “full description” of the chemistry, manufacturing, and controls for a drug should include “for example, tests” 21 C.F.R. § 314.50(d)(1)(i)–(ii).¹⁷ So the Court agrees with the determination made in connection with plaintiff’s motion for a preliminary injunction that FDA’s interpretation of section 355(b)(1)(D) to include immunogenicity testing was reasonable.

D. The statute did not require FDA to abandon the ANDA pathway and invoke section 355(b)(2).

Finally, contrary to Sanofi’s contentions, the ambiguity in the ANDA provisions is not clarified by the availability of section 355(b)(2), the quasi-third application pathway. Sanofi argues that the agency was bound to switch tracks to this “hybrid” drug approval method when the information submitted with Sandoz’s ANDA was found to be insufficient, but there is nothing in the statute that compels this approach. Indeed, if one reads the statute strictly, as Sanofi insists one should, there is nothing that would indicate that the (b)(2) pathway would have been applicable in this case at all; it appears to be more of a subset of NDA applications than a hybrid approach for a true generic.

Furthermore, as the Court noted in its opinion denying the motion for preliminary injunction, FDA’s reading of the statute accords with its own regulations on when (b)(2) is to be employed. *Sanofi-Aventis*, 733 F. Supp. 2d at 170–71. FDA’s approach is consistent with 21 C.F.R. § 314.54(a), which applies the 355(b) pathway for “[a]ny person seeking approval of a drug product *that represents a modification of a listed drug* (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval *of the changes[.]*” 21 C.F.R. § 314.54 (emphasis added). Here, FDA

¹⁷ See Tr. at 63, where counsel for FDA noted, “I mean, drug applications, particularly the CMC section, are practically nothing but test results.”

assessed Sandoz's generic drug as a replication of a listed drug, not a modification. Since 21 C.F.R. § 314.54(a) applies only for drug products that are modifications of listed drugs, it was not inconsistent with this regulation for FDA to decide to proceed under the (j) pathway rather than the (b)(2) pathway here.

FDA's determination of what constitutes a modification versus a replication of a listed drug is a scientific determination within the agency's area of expertise, and therefore is entitled to heightened deference from this Court. *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995) (“[C]ourts give a high level of deference to an agency's evaluations of scientific data within its area of expertise.”). While “there may well be more than one reasonable way to read” the word modification, it is not unreasonable for FDA to determine that a mere variance in the impurity profile of the drug is not a modification, and therefore, this Court is bound to uphold that interpretation. *See Serono*, 158 F.3d at 1321.

Sanofi further claims that allowing FDA to require immunogenicity data as part of an ANDA would render the (b)(2) pathway to be superfluous. Pl.'s Mem. at 30. But both the relevant FDA regulation, 21 C.F.R. § 314.54(a), and FDA guidance document show that is to be unlikely. As mentioned above, the section (b)(2) pathway is followed by new drug applicants who seek to rely on research conducted by a third party without that party's permission. FDA's regulations specify that this pathway covers “a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes[.]” 21 C.F.R. § 314.54. FDA's guidance document, “Applications Covered by Sections [355](b)(2),” clarifies that the kinds of modifications covered include changes in dosage form, strength, route of administration, or substitution of an active ingredient. *Guidance for Industry: Applications*

Covered by Section 505(b)(2) at 4 (2009),

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. While this guidance document is in no way binding on this Court, it does show that certain types of drugs undergo approval under section 355(b)(2) and will continue to undergo approval under that section even if generic drugs like Sandoz's enoxaparin are routed through the ANDA pathway in section (j). Therefore, this section is not rendered superfluous by FDA requiring immunogenicity data as part of an ANDA, and section 355(b)(2) does nothing to clarify Congress's intent as to section (j).

Since the statute is ambiguous as to whether FDA may require immunogenicity data and FDA's interpretation of the statute is reasonable, the Court finds that FDA did not exceed its authority by requiring Sandoz to submit comparative immunogenicity data as part of its ANDA.

II. FDA did not depart from agency precedent by approving a generic drug that is not fully characterized.

The next question at issue here – whether FDA departed from agency precedent by approving a generic version of enoxaparin without it being fully characterized – can also be decided on summary judgment because it is a pure question of law. Sanofi asks the Court to withdraw FDA's approval of Sandoz's generic enoxaparin because it approved the generic drug before enoxaparin was fully characterized. Sanofi alleges that this action departed from FDA precedent without reasoned explanation, in violation of the APA. Pl.'s Mem. at 31. In support of this claim, Sanofi repeats the argument that it asserted in its motion for preliminary injunction: that before FDA approved Sandoz's generic enoxaparin, it had refused to approve three other drugs – Premarin, Hyaluronidase, and Omnitrope – based on the fact that they had not yet been fully characterized, and that FDA failed to adequately explain why it departed from that precedent in approving Sandoz's drug. Pl.'s Mem. at 31–33.

Since Sanofi spends the majority of its summary judgment briefing arguing its first and third claims and does not assert any new arguments in support of this second claim, the Court finds no reason to diverge from the reasoning in the memorandum opinion denying the motion for a preliminary injunction on this Count, and it specifically incorporates that analysis here. *Sanofi-Aventis*, 733 F. Supp. 2d at 171–73.

The Court looks to whether the challenged agency decision was “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law.” *Sanofi-Aventis*, 733 F. Supp. 2d at 171, quoting 5 U.S.C. § 706(2)(A), citing *Motor Vehicle Mfrs. Ass’n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983). This Court’s review is “highly deferential” because the agency’s decision is based on the evaluation of complex scientific information within the agency’s technical expertise. *Id.* at 171–72, quoting *Bloch v. Powell*, 348 F.3d 1060, 1070 (D.C. Cir. 2003), citing *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997). In making its decision to approve Sandoz’s drug before it was fully characterized, FDA “provided ‘legitimate reason[s]’ for deciding that enoxaparin should be treated differently than the drugs cited by Sanofi” and therefore satisfied the minimal standard of rationality required. *Id.* at 172–73, citing *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 2007).¹⁸ As such, the Court will deny plaintiff’s motion for summary judgment as to Count II and grant defendants’ cross motion.

¹⁸ The Court is not certain that the agency’s handling of only three similar situations gives rise to the sort of precedent from which a departure needs to be justified, but it does not reach that question since the decision and the manner in which it diverged from previous decisions were adequately explained in this instance. Sanofi indicated that it would have objected even if there had only been one previous situation, so it appears that at bottom, its concern was more with the merits of the decision than with the agency’s consistency in any event. *See* Tr. at 41.

III. FDA sufficiently proved that Sandoz’s generic enoxaparin has the same active ingredient as Lovenox.

The final issue here – whether FDA sufficiently proved that Sandoz’s generic enoxaparin has the same active ingredient as Lovenox – can also be decided on summary judgment because it is a pure question law. Sanofi asks the Court to reverse FDA’s approval of Sandoz’s generic enoxaparin based on the way FDA determined active ingredient sameness.

As with Count II, the Court looks to whether FDA’s determination was “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law.” 5 U.S.C. § 706(2)(A); *see Motor Vehicle Mfrs. Ass’n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 41 (1983). The determination constitutes “an agency’s evaluation[] of scientific data within its area of expertise” and is therefore entitled to heightened deference by this Court. *A.L. Pharma*, 62 F.3d at 1490. Furthermore, the D.C. Circuit has already held that the validity of FDA’s interpretation of what makes a generic drug’s active ingredient “the same as” a listed drug’s active ingredient is a *Chevron* step II inquiry that deserves such heightened deference. *Serono*, 158 F.3d at 1319–20. “[T]he statute does not unambiguously require the term ‘same as’ to be defined as complete chemical identity.” *Id.* at 1320.

Sanofi picks at the third and fifth prongs of FDA’s five-pronged sameness test, but, as FDA argues, this attempt to invalidate an individual criterion for failing to show active ingredient sameness alone ignores FDA’s overarching five-pronged approach. FDA’s Mem. at 35. “Instead of relying solely on . . . any . . . single criterion, . . . FDA relied upon additional overlapping evidence derived from all five criteria” to show sameness. *Id.*

In criterion three, FDA required Sandoz to utilize direct sequencing techniques to compare the chemical makeup of the enoxaparin in Lovenox with the enoxaparin in Sandoz’s drug. AR 2897. However, rather than requiring Sandoz to sequence and compare all of the

sugar chains (oligosaccharide chains) that make up enoxaparin – which would require completely characterizing enoxaparin – FDA required it to sequence only a comparable subset of oligosaccharide chains. *Id.* The subset FDA chose included short chains, but excluded the longer chains. *Id.* FDA explained that these short sugar chains are “the result of the most cleavage reactions of the heparin oligosaccharide chains” and are therefore the most sensitive to variation in the process conditions used to make the drug.¹⁹ *Id.* Therefore, a showing that this subset of sugar chains from both the generic drug and Lovenox possess the same sequence “provides further corroborative evidence that the generic drug product’s enoxaparin possesses the same distribution of oligosaccharide sequences as Lovenox’s enoxaparin” and is therefore the same. *Id.*

Clearly this factor alone is insufficient to show active ingredient sameness because it does not show complete equivalence of the two active ingredients. But, FDA did not rely on sequencing alone to determine active ingredient sameness; rather, it was one of five factors that FDA considered together. FDA concluded that “[t]hese five criteria together comprise a robust test that provides overlapping evidence by which an ANDA applicant for enoxaparin can demonstrate active ingredient sameness for enoxaparin within the meaning of [21 U.S.C. § 355(j)] and FDA regulations.” AR 2880. Thus, by selecting only certain sugar chains for Sandoz to sequence, FDA did not allow Sandoz to take a “short cut” to sequencing all of the sugar chains, as Sanofi asserts, but FDA defined what was necessary to satisfy prong three of the sameness test, given the information required under the other four prongs. *See* Pl.’s Mem. at 36.

¹⁹ Sanofi contests FDA’s assertion that the short sugar chains are the result of the most cleavage reactions. Pl.’s Mem. at 39–41. However, given that FDA supports its assertion in the record, *see* AR 2890, 2894–95, 2897, and given the high level of deference the Court must accord FDA here, the Court cannot find that FDA’s conclusion is unreasonable, *see* 5 U.S.C. § 706(2)(A); *see also Motor Vehicle Mfrs. Ass’n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 41 (1983).

In addition, Sanofi cannot show that Sandoz failed to satisfy factor five of the sameness test. In so arguing, Sanofi actually misstates factor five. According to Sanofi, that factor required Sandoz to show the full equivalence of the in vivo pharmacodynamics profiles (*i.e.*, equivalent action or effect in the body) between its generic drug and Lovenox. *Id.* at 42–43. Sanofi claims that Sandoz failed to satisfy this because it showed equivalence only of its effect on two factors (anti-Xa and anti-IIa), but not of its effect on a third (TFPI). *Id.*

However, nowhere in the administrative record does FDA claim that prong five requires a generic enoxaparin manufacturer to show full equivalence of in vivo pharmacodynamics profiles between its drug and Lovenox. Although in FDA’s response letter to Sanofi’s citizen petition, criterion five is titled, “Equivalence of In Vivo Pharmacodynamics Profile,” the body of the letter explains that “[t]he comparison of in vivo pharmacodynamics profiles is based upon measurements of in vivo anti-Xa and anti-IIa profiles.” AR 2899.

Furthermore, given the high level of deference this Court must accord FDA’s determination, Sanofi does not persuade the Court that it was unreasonable for FDA to focus only on anti-Xa and anti IIa. Although it may be true that “enoxaparin’s effect on TFPI is a part of its overall pharmacodynamics profile[,]” Pl.’s Mem. at 42, FDA chose anti-Xa and anti IIa as the most important factors, AR 2899. FDA therefore, could reasonably have decided that if Sandoz could show that the effect of its drug on the two most important factors was equivalent to Lovenox, then it did not need to further show that the effect on a less important factor was equivalent. This is particularly true given the “overlapping” nature of the five prongs in the sameness test.

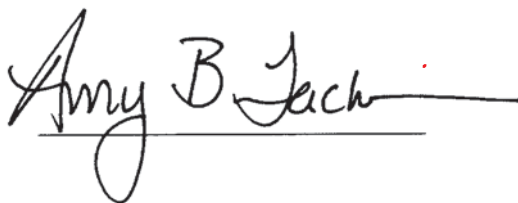
Thus, the Court’s analysis turns on whether the five-pronged approach itself was a reasonable way for FDA to determine active ingredient sameness. Not only did FDA support its

approach in a thorough, well-reasoned response to Sanofi’s citizen petition, but it also carefully considered both sides of the argument internally – to settle the internal dispute over the validity of the five-pronged test – before doing so. AR 3836–48, 3853–61. “Of course, differing views among an agency’s staff may indicate that there is more than one reasonable way to read a statute. . . . But under *Chevron*, courts are bound to uphold an agency interpretation as long as it is reasonable – regardless whether there may be other reasonable, or even more reasonable, views.” *Serono*, 158 F.3d at 1321. While fully characterizing enoxaparin would have been another reasonable, or perhaps even more reasonable, way to determine active ingredient sameness, the Court is satisfied that the five-pronged approach FDA used was reasonable.

The Court is further convinced that the reason FDA required immunogenicity testing was to determine whether the drug contained harmful impurities, not to settle a last minute worry that the five criteria were insufficient to establish sameness. FDA has represented all along that it sought the immunogenicity data in order to determine whether the generic drug contained potentially harmful impurities. *See* AR 3849–50, 4193–94, 4433–34. And that is exactly what the immunogenicity data Sandoz submitted actually told FDA. AR 4433–35. Perhaps it would have also been rational for FDA to require immunogenicity data to show whether its generic drug contained the same active ingredient as Lovenox. However, that is not why FDA required the data here.

CONCLUSION

Because FDA's request for immunogenicity data in Sandoz's ANDA was both lawful and reasonable, its approval of the drug did not constitute an arbitrary departure from agency precedent, and its determination of active ingredient sameness was not arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with the law, the Court will grant defendants' motions for summary judgment and deny plaintiff's cross-motion.

A handwritten signature in black ink, reading "Amy B. Jackson", written over a horizontal line. The signature is cursive and stylized.

AMY BERMAN JACKSON
United States District Judge

DATE: February 7, 2012